

CLAIMS

- ✓ 1. A modified animal or avian species exhibiting reduced levels of a Bcl-w protein and/or protein associated with Bcl-w or a derivative or homologue thereof, wherein said animal or avian species has an incapacity or a reduced capacity to induce or facilitate spermatogenesis.
2. A modified animal or avian species according to claim 1 wherein the Bcl-w protein comprises an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 or is an amino acid sequence having at least about 47% similarity thereto.
3. A modified animal or avian species according to claim 2 wherein the Bcl-2 is encoded by a nucleotide sequence substantially as set forth in SEQ ID NO: 1 or SEQ ID NO: 3 or is a nucleotide sequence having at least about 47% similarity thereto or is a nucleotide sequence capable of hybridizing to SEQ ID NO: 1 or SEQ ID NO: 3 under low stringency conditions of 42°C.
4. A modified animal or avian species according to claim 1 wherein a protein associated with Bcl-2 is encoded by a gene which is approximately 9.2 kb downstream of *bcl-w* exon 3.
5. A modified animal or avian species according to claim 4 wherein the gene downstream of *bcl-w* is homologous to the *Drosophila rox* gene.
6. A modified animal or avian species according to any one of claims 1 to 5 wherein the modified animal or avian species comprises an introduced antagonist of Bcl-w activity.
7. A modified animal or avian species according to claim 6 wherein the antagonist is an antibody or a Bcl-w binding portion thereof.
8. A modified animal or avian species according to claim 6 wherein the antagonist is a molecule comprising a Bcl-2 Homology (BH) 3 motif.

00508745-074200

9. A modified animal or avian species according to any one of claims 1 to 5 wherein the modified animal comprises a deletion in the *bcl-w* gene.
10. A modified animal or avian species according to any one of claims 1 to 5 wherein the modified animal comprises an introduced genetic molecule capable of inhibiting or reducing exposure of the *bcl-w* gene.
11. A modified animal or avian species according to claim 10 wherein the genetic molecule is an antisense molecule capable of hybridizing to all or part of a mRNA transcription of *bcl-w*.
12. A genetically modified animal comprising a mutation in one or more alleles of a gene comprising a sequence of nucleotides substantially as set forth in SEQ ID NO: 1 or SEQ ID NO: 3 or a nucleotide sequence having at least about 47% similarity thereto and/or a sequence which is capable of hybridizing to SEQ ID NO: 1 or SEQ ID NO: 3 under low stringency conditions at 42°C.
13. A genetically modified animal according to claim 12 comprising a mutation in both alleles of the gene.
14. A method of producing a genetically modified animal substantially incapable of producing Bcl-w, said method comprising introducing a genetic sequence into embryonic stem (ES) cells, which genetic sequence targets the *bcl-w* gene or a transcript thereof or a gene associated with *bcl-w* and introducing said ES cells into blastocysts to produce a chimeric animal.
15. A method according to claim 14 wherein the genetically modified animal is a mouse.
16. A method according to claim 14 or 15 wherein the introduced genetic sequence is an antisense molecule, encoding an antisense molecule or permits excision of the *bcl-w* gene or a region within the *bcl-w* gene.

- 42 -

17. A method according to claim 16 wherein the introduced genetic sequence encodes the Cre recombinase.

✓ 18. A modified animal comprising a mutation in a gene corresponding to *bcl-w* or a derivative or homologue thereof or in a gene associated with *bcl-w* wherein an adult male of said animal exhibits the following characteristics:

- (i) is substantially infertile;
- (ii) possesses disorganised seminiferous tubules;
- (iii) exhibits heterogenous degeneration of germ cell types; and
- (iv) possesses no other major abnormalities as determined by histological examination.

19. A modified animal according to claim 18 wherein the *bcl-w* mutation is on chromosome 14q11.

✓ 20. A modified animal or avian species exhibiting reduced levels of a Bcl-w protein having an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:4 or a Bcl-w protein encoded by a nucleotide sequence substantially set forth in SEQ ID NO:1 or SEQ ID NO:3 or a nucleotide sequence capable of hybridising to SEQ ID NO:1 or 3 or 5 or 7 under low stringency conditions at 42 °C wherein said animal or avian species has an incapacity or a reduced capacity to induce or facilitate spermatogenesis.

00506245-074000